DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

2089d

November 2, 2001

WARNING LETTER
CHI-6-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Harry J. Kraemer, Jr.
President & CEO
Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015

Dear Mr. Kraemer:

From August 7 through August 17, 2001, an inspection of the Baxter Healthcare Corporation laboratory facility located at Route 120 and Wilson Road, Round Lake, IL, was conducted by Investigator Susan P. Bruederle. The inspection documented deviations from the Current Good Manufacturing Practice Regulations (cGMPs) for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. Those deviations cause drug products tested at your facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (The Act). The deviations were presented to Karen L. Malik, Senior Director, Stability Operations and Pharmaceutical Technology, on the Form FDA-483, Inspectional Observations, at the close of the inspection. A copy of the FDA-483 is enclosed. Deficiencies noted include, but are not limited to, the following:

Failure to establish laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality, and purity [21CFR 211.160(b)] and failure to design a written testing program that enables the assessment of the stability characteristics of drug products [21 CFR 211.166 (a)]. Examples of these deviations are:

- Stability studies for the drugs [redacted] (ANDA [redacted]) and [redacted] (NDA [redacted]), include test results in the stability summary tables that are averages of multiple tests and in some instances the average includes out-of-specification (OOS) results. For example:

  a. Stability study #1999275, 25°, 18-month interval. The value reported on the stability sheet for color is an average of [redacted] One of the units exceeded the specification for color.
  b. Stability study #1999291, 40°, 2 month interval. The value reported on the stability sheet for color is an average of [redacted] One of the units exceeded the specification for color.

c. Stability study #1999384, 40°, 3 month interval ([redacted]). The chloride test result listed on the stability summary sheet is an average of [redacted] individual values, one of which is below specifications.

d. Stability study #1999384, 25°, 9 month and 30°, 9 month intervals ([redacted]). The results of the molecular weight distribution tests listed in the stability summary sheets are averages of [redacted] One value is below specifications.

Failure to conduct a thorough investigation of any unexplained discrepancy or failure of a batch to meet its specification [21 CFR 211.192]. For example:

- Laboratory Investigation Reports (LIR) reviewed in some instances indicated that no further action was required if the average of the retest results and OOS result(s) is within acceptable limits even if the OOS result is determined to be valid by data review and investigation. For example:

  a. Laboratory Investigation Report IN 766 covered the drug [redacted] and [redacted], Batch PS079459. This test was performed under the Stability Study #1999019, 25° at the 12 month test interval. The result of the theophylline assay performed on 12/2/99 exceeded limits. The data review found no reason to invalidate the OOS result. Two analysts tested two other units. The average of the five test results was within limits.

  b. Laboratory Investigation Report IN 876 covered the drug product [redacted], Lot CA70393, Stability Study 2000180, 25°, at the 6 month test interval. The result of the sodium assay performed on 1/24/01 exceeded limits. The data review found no reason to invalidate the OOS result. The original unit was retested. In addition, two analysts tested two other units. The Investigation Report concludes, "Interval average within limits – no further action required."

- The OOS test results for the [redacted] assay performed on 12/8/00 for the 5°, 21 day short term testing at the 18 month stability test interval were invalidated although there was no documented evidence of an analytical error. Laboratory Investigation Report IN 870, which covers this matter, indicated that no problems were found in the review and investigation of the data. All system suitability requirements were reported to have been met. However, an attachment to the LIR states: "The original data will be excluded from interval average. This assay normally performs with better precision and accuracy than is demonstrated in the initial run, possibly due to inexperience of the analyst with this method."

We acknowledge receipt of the written response to the FDA-483, dated August 28, 2001, that was submitted by Ms. Malik and addresses the inspectional observations on the Form FDA-483 issued at the close of the inspection. We have reviewed the contents of the response. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. Our comments are detailed below:

Items #1 & 3

In the response, Ms. Malik states that Baxter commits to clearly indicate when averages are reported and to provide discussion of all OOS data that are included in a reported average. FDA item #1 pertains to information submitted in the NDA for "[redacted]" (NDA [redacted]) while FDA item #3 pertains to information submitted in the ANDA for "[redacted]" (ANDA [redacted]). For both applications, Baxter indicates that this information will be provided to the FDA in future submissions. The instant inspection revealed that the stability data submitted for NDA [redacted] includes averages of [redacted] to [redacted] individual test results. No information was provided in this response on what Baxter plans to do relative to information such as this for applications such as the two discussed above that have been previously submitted to the FDA.

Item #2

This FDA-483 observation addresses the fact that actual test intervals are not accurately reported for the test intervals for Stability Study 1999384 in the NDA [redacted] submission. Baxter's written response states that "a discussion of any testing that is significantly delayed, i.e., more than 30 days from the scheduled test date, will be provided, and, if appropriate, an additional test interval will be added to the test schedule." As with our comments on the response to FDA items #1 & 3, no comment is provided on what action Baxter will take relative to data that FDA is currently reviewing for this application.

Item #4

The corrective action Baxter indicates it has taken for this FDA-483 observation is the revision of SOP, SP-12-02-002, "Stability Data Review and Out of Limits Reporting Process," in order to ensure adequate documentation of the final disposition of an investigation. A copy of this SOP was furnished with the response. This revised procedure does not require that an investigation be conducted to determine the cause of the stability test failure. Also, the SOP does not discuss whether any action, such as extending the investigation to the investigation site or notifying other units in Baxter if the OOS test result is not confirmed by retesting, even if the original test is considered valid.

Item #5

The response indicates that Baxter's investigation revealed that the original test lacked appropriate precision and accuracy and the cause of the OOS data is analytical error. The FDA-483 item indicated there was no documented evidence of an analytical error in the [redacted] assay. The response does not indicate whether there is any documented evidence of the analytical error. The response also indicates that the invalidated results remain in the stability study database. However, Investigator Bruederle was provided a copy of the database printout for this stability study during the inspection. The document given to Investigator Bruederle does not include the results of the original tests. The word "INVALID" is listed for the original test results.

Item #6

We will review the records of the investigation during the next inspection.

Items #7 & 8

We have no additional comments on the response to these items.

Neither this letter nor the inspectional observations (Form FDA-483) is meant to be an all-inclusive list of deficiencies that may exist at your firm. It is your responsibility to assure adherence with each requirement of the cGMPs. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt measures to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include, but are not limited to, seizure and/or injunction.

I have received your letter dated October 31, 2001, in which you request a meeting to discuss the results of the inspection. We will be happy to meet with you. I will be available for a meeting on November 13 or 14, 2001. Please call Richard Harrison, Director, Compliance Branch, relative to this meeting date.

Please notify this office within 15 days of receipt of this letter, of the specific steps you will take to comply with our request. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Your response should be sent to the attention of George F. Bailey, Compliance Officer, at the above address.

Sincerely,

\s\
Raymond V. Mlecko
District Director

cc: John Quick, Corporate VP
Regulatory and Quality,
Route 120 and Wilson Road
Round Lake, Illinois 60073